The Dilemma of Renin Angiotensin System Blockers in Coronavirus Disease (Covid-19): Insights on the Lung Fluid Handling and Gas Exchange in Heart Failure Patients

Viewpoint Paper

Marco Guazzi, MD, PhD, Alice Moroni, MD

From the Cardiology University Department, IRCCS Policlinico San Donato, University of Milano, Milano, Italy

No conflict of interest exists for all authors

Address for Correspondence

Marco Guazzi, MD, PhD, FESC, FACC, FAHA
University of Milano
Department of Biomedical Sciences for Health
Heart Failure Unit-Cardiology
IRCCS Policlinico San Donato
Piazza E. Malan 2, 20097
San Donato Milanese, Milano
ITALY
Tel and Fax: +39 02 52774966
Email: marco.guazzi@unimi.it

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.1910.

The coronavirus disease 2019 (Covid-19) pandemic is precipitating the global health crisis of our time, as stated by the World Health Organization (WHO). Since it surge in December 2019, in Wuhan, Hubei province, China, the virus has spread to every continent except Antarctica. The main clinical manifestation of SARS-CoV-2 is severe acute respiratory syndrome which yields to inflammatory reaction and alveolar fluid floading ultimately impairing gas exchange. [1-3]

Reports have clearly established that hypertension, diabetes, and cardiovascular diseases are the most frequent comorbidities in affected patients, and these individuals are exposed to the highest mortality rates. [4, 5]

Most of these patients suffer from already preexistent or rapidly evolving heart failure (HF) [6, 7] and they are commonly treated with renin angiotensin system blockers, such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as Guidelines Class I, Level of Evidence A. [8] However, there is an ongoing debate about the use of ACEIs/ARBs in patients with Covid-19 or at risk of SARS-CoV-2 infection which may not be beneficial or even harmful. [9] Vaduganathan et al [10] have recently reported an elegant and comprehensive revision on the controversial aspects of this topic providing the most updated evidence.

We gained previous experience on the effects of renin-angiotensin system inhibition on the pulmonary function of HF patients showing a protective effect on the perturbed gas exchange and lung fluid handling, i.e. alveolar capillary stress-failure, an effect especially observed with enalapril treatment, with a positive but statistically not signfiicnat trend for losartan [11, 12] .

Based on this, we outline how renin angiotensin blockers may interact with the lung fluid handling and gas diffusion process in patients with HF infected by SARS-CoV-2, and propose areas for further research.

Both ACE and ACE2 are homologous enzymes part of the ACE family of the dipeptidyl and monopeptidyl carboxydipeptidases, respectively, with different key functions in the renin angiotensin system. ACE cleaves angiotensin (Ang) I to angiotensin (Ang) II, which in turn binds and activates Ang II receptors type 1 and type 2. Activation of type 1 receptors leads to vasoconstrictive, proinflammatory, and pro-oxidative effects. ACE2 cleaves Ang I to Ang-(1-9) and to Ang-(1-7). ACE2 also mediates the conversion of Ang II to Ang-(1-7) which binds to the Mas receptor and promotes anti-inflammatory, antioxidative, and vasodilatory effects. [13]

All these effects are well studied and documented for the systemic circulation, but information regarding their activity on the pulmonary microcirculation are mostly lacking.

Interestingly, ACE is produced in the lung tissue and released by the pulmonary circulation. In humans, ACE2 is predominantly expressed in the alveolar Type II cells and enterocytes of the small intestine. [14]

SARS-CoV-2 utilizes lung ACE2 as an essential receptor for cell entry and host cellular proteases into the alveolar Type II cells. Namely, the spike (S) protein of SARS-CoV-2 is primed by a transmembrane cellular serine protease, TMPRSS2 2, which allows fusion of viral and cellular membranes. [15]

Physiologically, fluid handling across the alveolar gas barrier is modulated by cellular and molecular mechanisms of ions and fluid transposition as depicted in the Figure. The alveolar surface is continuously cleared by the excess of fluid through the activity of energy-independent epithelial sodium channels (eNaC) and acquaporins. [16] Fluid is then transposed by ATP Na^+/K^+ pumps into the vascular compartment. These protective pathways, which are essential to keep the alveolar surface dry and guarantee gas exchange, are highly challenged by a number of hemodynamic, inflammatory and growth factor stimuli typical of HF syndrome. [3, 17] Interstitial fibrosis and capillary remodeling ensue when the fluid triggers the inflammatory cascade and connective tissue reaction. [18] In HF with pulmonary congestion and inflammation and even some reactive interstitial fibrosis, renin angiotensin system blockade by ACEI has been shown to promote a protective effect on lung fluid swelling from capillaries to interstitium and "speed-up" the fluid clearance during saline loading with improved gas exchange. [11, 12, 19]

The infection by SARS-CoV-2 specifically challenges and disrupts the fine protective mechanisms of ion regulatory transport and precipitate the edematous-inflammatory cascade.[20]

Renin angiotensin system blockade increases the ACE2 overexpression and in SARS-CoV-2 free conditions there is a strong rationale that ACE2 may mediate these beneficial effects. [21, 22]

Thus, in conditions of SARS-CoV-2 infection the ACE2 activity appears downregulated yielding to an unfavorable Ang II/Ang-(1-7) balance. [23] Of note, Ang-(1-7) plays a crucial protective role against lung inflammation. Specifically, this heptapeptide inhibits alveolar apoptosis, limits the synthesis of cytokines and attenuates endothelial cell activation and the loss of barrier function and oedema. [24]

Experimental models of genetically-modified mice undergoing acute lung injury have documented an ACE2 protein downregulation by binding its spike protein and this loss leads to a leaky capillary effect through stimulation of AT1 receptors. [25] Interestingly enough, the ACE2 knockout strain exhibited the worse edematous and inflammatory response and pretreatment

with exogenous recombinant human ACE2 attenuated acute lung failure in ACE2 knockout as well as in the wild-type mice. [25]

Additional experimental observations looking at hyperoxia treatment showed significant reduction in lung ACE2 expression/activity and increased Ang II/Ang-(1-7) ratio in adult mice exposed to 95% O_2 for 72 h. It has also been demonstrated that activation of ACE2 can reduce the severity of hyperoxic lung injury by inhibiting inflammatory response and oxidative stress and that ACE2 can inhibit the NF-κB and activate the Nrf2/HO-1/NQO1 pathways, which may be involved in the underlying mechanism. [26] A pre Covid-19 trial of ACE2 infusion in 10 patients with acute respiratory distress syndrome was completed in humans but was not powered to show efficacy on gas exchange. [27]

A main question, however, is whether the SARS-CoV-2 ability to neutralize ACE2 activity could be so powerful to neutralize the additive protection of ACE2 overexpression, definitively leading to an untoward negative cascade of lung fluid compartimentalization, ventilation/perfusion mismatch and impaired gas exchange.

This key issue will be likely clarified soon but, meanwhile, reasoning on this double edge front, it is tempting to speculate that ARBs could divert a larger amount of angiotensin II to the ACE2 activity, even though it remains unpredictable what level of benefit or harm could be observed with ARBs versus ACEIs.

In the rapidly evolving scenario of pandemia, the present observations could enhance our understanding on how treatment with renin angiotensin system blockers may impact Covid-19 HF patients.

Accordingly, we highly advocate that upcoming basic science and clinical proof of concept studies should scrutinize the aforementioned working hypotheses and theories.

On one hand, preclinical studies should be planned for definitively establishing the interaction between molecular pathways involved in the alveolar-capillary fluid handling and ACE2 activity in knockout ACE2 -/- versus ACE2 +/+ animal models of SAR-CoV-2 lung injury.

On the other hand, clinical studies should recruit SARS-CoV-2 asymptomatic carriers to test how the inhibition of renin angiotensin system, by randomization to ACE-I or ARB, could impact on the fluid homeostasis and gas exchange processes by mitigating or worsening their fundamental physiology, peculiarly threatened by the SARS-CoV-2 infection.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS and China Medical Treatment Expert Group for C. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020.
2. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, Enouf V, Houhou-Fidouh N, Valette M, Mailles A, Lucet JC, Mentre F, Duval X, Descamps D, Malvy D, Timsit JF, Lina B, van-der-Werf S and Yazdanpanah Y. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis*. 2020.
3. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. *J Card Fail*. 2008;14:695-702.
4. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J and Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020.
5. Wang L, He W, Yu X, Hu D, Bao M, Liu H, Zhou J and Jiang H. Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020.
6. Chen L, Li X, Chen M, Feng Y and Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020.
7. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM and Metra M. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P and Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129-2200.
9. Sommerstein R GC. Re: Preventing a covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. *BMJ*. 2020;368:m810.
10. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA and Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med*. 2020.
11. Guazzi M, Marenzi G, Alimento M, Contini M and Agostoni P. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation*. 1997;95:1930-6.
12. Guazzi M, Agostoni P and Guazzi MD. Modulation of alveolar-capillary sodium handling as a mechanism of protection of gas transfer by enalapril, and not by losartan, in chronic heart failure. *J Am Coll Cardiol*. 2001;37:398-406.
13. Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM and Bader M. The renin-angiotensin system: going beyond the classical paradigms. *Am J Physiol Heart Circ Physiol*. 2019;316:H958-H970.

14. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G and van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631-7.
15. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C and Pohlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020.
16. Matthay MA, Folkesson HG and Verkman AS. Salt and water transport across alveolar and distal airway epithelia in the adult lung. *Am J Physiol*. 1996;270:L487-503.
17. Verbrugge FH, Guazzi M, Testani J, Borlaug B. Altered hemodynamics and end-organ damage in heart failure: impact on the lung and the kidney. *Circulation*. 2020;in press.
18. Guazzi M, Phillips SA, Arena R and Lavie CJ. Endothelial dysfunction and lung capillary injury in cardiovascular diseases. *Prog Cardiovasc Dis*. 2015;57:454-62.
19. Guazzi M, Brambilla R, Agostoni P and Guazzi MD. Influence of ACE-inhibition on salt-mediated worsening of pulmonary gas exchange in heart failure. *Br J Clin Pharmacol*. 2001;51:482-7.
20. Peteranderl C, Sznajder JI, Herold S and Lecuona E. Inflammatory Responses Regulating Alveolar Ion Transport during Pulmonary Infections. *Front Immunol*. 2017;8:446.
21. Deng J, Wang DX, Deng W, Li CY and Tong J. The effect of endogenous angiotensin II on alveolar fluid clearance in rats with acute lung injury. *Can Respir J*. 2012;19:311-8.
22. Shenoy V, Ferreira AJ, Qi Y, Fraga-Silva RA, Diez-Freire C, Dooies A, Jun JY, Sriramula S, Mariappan N, Pourang D, Venugopal CS, Francis J, Reudelhuber T, Santos RA, Patel JM, Raizada MK and Katovich MJ. The angiotensin-converting enzyme 2/angiogenesis-(1-7)/Mas axis confers cardiopulmonary protection against lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med*. 2010;182:1065-72.
23. Peiro C and Moncada S. Substituting Angiotensin-(1-7) to Prevent Lung Damage in SARSCoV2 Infection? *Circulation*. 2020.
24. Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M and Campagnole-Santos MJ. The ACE2/Angiotensin-(1-7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1-7). *Physiol Rev*. 2018;98:505-553.
25. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C and Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436:112-6.
26. Fang Y, Gao F and Liu Z. Angiotensin-converting enzyme 2 attenuates inflammatory response and oxidative stress in hyperoxic lung injury by regulating NF-kappaB and Nrf2 pathways. *QJM*. 2019;112:914-924.
27. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI and Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Crit Care*. 2017;21:234.

Figure Legend- ***Schematic representation of fluid handling trough the alveolar-capillary barrier and potential effects of RAS-system inhibition and ACE2 levels in the normal and Covid-19 condition***

Fluid is continuously removed from the alveoli (type II pneumocytes) to the interstitium by the epithelial Na^+ channels (eNaC) and acquaporins. Then removal of fluid from the intertistium to the vascular compartment is driven by osmosis and Na^+/K^+ ATPase pump. These mechanisms are essential for guarantee an efficient gas exchange. Multiple conditions, and primarily HF, challenge the integrity of the alveolar-capillary unit and the functional response of these molecular mechanisms. The best in vivo method to assess how these systems work is measuring gas exchange.

Studies performed in HF patients under treatment with renin angiotensin system blockade, especially ACEI, investigating the gas exchange response under fluid loading have shown a facilitating effect on the on alveolar capillary membrane gas diffusion. This effect would be mediated by high ACE2-induced Ang-(1-7) production and low Angio II.

SARS-CoV-2 binds to ACE2 for entering and injury the type II cells leading to an inflammatory reaction and cytokines release. ACE2 expression activity is down-regulated in experimental models of ARDS and overexpression of ACE2 in null models is beneficial.

RAS-inhibitors (ACEIs and primarily ARBs) stimulate ACE2 synthesis and Ang II conversion to Ang-(1-7) which may be of benefit or even harmful according to the degree of affinity and the reciprocal neutralizing effects between ACE2 and SARS-CoV-2.